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(54) Title: DRY POWDER COMPOSITIONS

(57) Abstract: A hydrophilic therapeutic agent is prepared in storage-stable form, suitable for administration to a patient. The agent is formulated with a hydrophobically-derivatised carbohydrate, making use of ion-pair formation to form a solution of the agent and carbohydrate.

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**DRY POWDER COMPOSITIONS**Field of the Invention

This invention relates to the production of stabilised  
5 therapeutic agents, prepared using hydrophobically-  
derivatised carbohydrates, and to therapeutic compositions.

Background to the Invention

Numerous therapeutic proteins and peptides are  
currently available for clinical use. A variety of  
10 delivery methods and routes exist, of which the parenteral  
route is the most widely used. Delivery via the pulmonary  
route is an attractive alternative mainly due to  
acceptability by patients. There is also evidence to  
suggest that relatively large molecules such as proteins  
15 can be absorbed readily across the lung surface and into  
the blood stream. Techniques for pulmonary delivery are  
still in the early stages of development, and as a result,  
considerable scope for new pulmonary formulations of  
therapeutic proteins and peptides exists.

20 One way of formulating therapeutic proteins is by the  
use of carbohydrates, which act to stabilise the proteins  
during storage and also aid delivery. An example of a  
stabilising carbohydrate is trehalose.

Recently, there has been interest in using  
25 hydrophobically-derivatised carbohydrates (HDCs) in  
formulating proteins. WO-A-96/03978 discloses compositions  
comprising a HDC and therapeutic agent, formulated into  
solid dose form for direct delivery. The compositions may  
be powders for pulmonary delivery, microneedles or  
30 microparticles for ballistic, transdermal delivery or  
implantable compositions.

The advantage in having a therapeutic agent formulated  
with a HDC, is that there is the potential for developing  
controlled release delivery systems. In addition, the HDC  
35 may itself have desirable properties that aid delivery, in  
particular to the deep lung.

However, therapeutic proteins are generally hydrophilic, and due to the hydrophobicity of HDC molecules, the incorporation of proteins into HDCs is problematic.

5        There is therefore a need for an efficient process by which hydrophilic agents can be incorporated into HDCs.

Summary of the Invention

10        The present invention is based on the realisation that hydrophilic agents can be incorporated efficiently into HDCs by the use of hydrophobic ion-pairing (HIP).

15        According to a first aspect of the present invention, a method for the preparation of a therapeutic composition, comprises forming a solution, in an organic solvent, of a hydrophobically-derivatised carbohydrate and an ion-pair complex of a hydrophilic therapeutic agent and an ionic substance; and drying the solution.

In one embodiment, the method comprises the steps of:

- 20        (i)    mixing the therapeutic agent with the ionic substance, in an aqueous medium, to form a precipitate;
- (ii)   dissolving the precipitate and the HDC in an organic solvent; and
- (iii)  drying the resulting organic solution.

25        In a further embodiment, the method comprises the steps of:

- (i)    mixing the therapeutic agent in aqueous solution with the ionic substance to form the ion-pair complex;
- 30        (ii)   adding a water-immiscible organic solvent to form an organic phase, and allowing the ion-pair complex to pass into the organic phase;
- (iii)  separating the organic phase;
- (iv)   adding the HDC to the organic phase; and
- (v)   drying the resulting organic solution.

35        According to a second aspect, a composition comprises, in solid dose form, a hydrophobically-derivatised

carbohydrate, a therapeutic agent and a pharmaceutically acceptable ionic detergent.

According to a third aspect, compositions of the invention may be used in the manufacture of a medicament to be administered to a patient via the pulmonary route, for the treatment of a disease.

The products are intended for therapeutic use, and the active agent will be therapeutically active on delivery.

The effective incorporation of a hydrophilic agent into the HDC provides useful therapeutics to be formulated with desirable controlled release properties.

#### Description of the Invention

The method according to the present invention is based on the realisation that hydrophobic ion-pairing is a useful method applicable to formulating a hydrophilic agent with a hydrophobic carbohydrate.

In summary, the procedure involves generating hydrophobic ion-pairs between positive charges on the actives, e.g. proteins, and negative charges on selected anionic surfactants. Alternatively, the polarity of the charges on the protein and surfactant can be reversed.

The present method may be carried out under conditions known to those skilled in the art. It is well known that hydrophilic proteins can be precipitated out of solution using low concentrations of an anionic detergent. It appears that precipitation is the result of displacement by the detergent of counter-ions from the ion-pairs on the protein. The precipitate may then be isolated by, for example, centrifugation, and then subsequently dissolved in an organic solvent containing the HDC. The hydrophilic agent is then in solution with the HDC and can be dried to form a solid. The total recovery of the active is high, and consequently, the present method offers a commercial scale process to be developed.

Alternatively, the ion-pair may be formed without a precipitate, by phase separation. A protein in an aqueous phase is mixed with a suitable detergent to form an

ion-pair. A suitable organic solvent is added to form an organic phase, and the ion-pair complex is allowed to incorporate into the organic phase. The organic phase may then be separated and mixed with the HDC, optionally  
5 comprised within a further organic solvent.

#### *Hydrophilic agents*

The hydrophilic agents that may be used in the present invention include any therapeutically active protein, peptide, polynucleotide or ionic drug. In particular, the  
10 agent may be an enzyme or a hormone. Examples include, but are not limited to, insulin, interferons, growth factors,  $\alpha$ -chymotrypsin interleukins, calcitonin, growth hormones, leuprolide, colony-stimulating factors and DNase. Insulin is a preferred embodiment, and is a desirable therapeutic  
15 for pulmonary delivery.

#### *Ionic substances*

Any suitable ionic substance may be used in the invention. A preferred substance is a detergent. The substance is preferably anionic when proteins or peptides  
20 are to be incorporated into the HDCs. When polynucleotides or negatively charged proteins are the active agent, the substance should preferably be cationic. Suitable anionic substances include salts, e.g. sulphates, sulphonates, phosphates and carboxylates.

25 Examples of suitable anionic detergents include sodium dodocyl sulphate (SDS), sodium docusate (AOT), phosphatidylinositol (PPI), 1,2-dipalmitoyl-sn-glycero-3-phosphatidic acid sodium salt (DPPA.Na), 1,2-dipalmitoyl-sn-glycero-3-phosphoglycerol sodium salt (DPPG.Na) and  
30 sodium oleate. Examples of suitable cationic detergents include benzalkonium chloride (BAC), hexadecyltrimethylammonium bromide (CTAB) and dodecyltrimethylammonium bromide (DoTAB).

Preferably, the detergent should be pharmaceutically  
35 acceptable. In particular, the detergent should be suitable for pulmonary delivery.

*Organic solvents*

Any suitable organic solvent may be used in the present invention. Polar or non-polar solvents may be used depending on the active agent. In general, the solvent will be one that is pharmaceutically acceptable. Suitable solvents include, but are not limited to, ethanol, propanol, isopropanol, 1-octanol, acetone, ether, ethyl acetate, ethyl formate, dichloromethane (DCM), hexane and methanol.

10 *Hydrophobically-derivatised carbohydrates (HDCs)*

The HDC may be any of those known in the art. Preferably, the HDC forms an amorphous glass with a high Tg, on drying.

Preferably, the HDC is capable of forming a glass with a Tg greater than 20°C, more preferably greater than 30°C, and most preferably greater than 40°C.

As used herein, "HDC" refers to a wide variety of hydrophobically-derivatised carbohydrates where at least one hydroxyl group is substituted with a hydrophobic moiety including, but not limited to, esters and ethers.

Numerous examples of suitable HDCs are described in WO-A-96/03978 and WO-A-99/01463. Specific examples of HDCs include, but are not limited to, sorbitol hexaacetate (SHAC),  $\alpha$ -glucose pentaacetate ( $\alpha$ -GPAC),  $\beta$ -glucose pentaacetate ( $\beta$ -GPAC), 1-O-octyl- $\beta$ -D-glucose tetraacetate (OGTA), trehalose octaacetate (TOAC), trehalose octapropanoate (TOPR),  $\beta$ -4',6'-diisobutyroyl hexaacetyl lactose, sucrose octaacetate (SOAC), cellobiose octaacetate (COAC), raffinose undecaacetate (RUDA), sucrose octapropanoate, cellobiose octapropanoate, raffinose undecapropanoate, tetra-O-methyl trehalose, di-O-methyl-hexa-O-acetyl sucrose, and trehalose 6,6-diisobutyrate hexaacetate.

Pure single HDC glasses have been found to be stable at ambient temperatures and up to at least 60% humidity. Mixtures of HDC glasses incorporating certain active substances are, however, surprisingly stable at ambient

temperatures and up to at least 95% humidity. Mixtures of different HDCs may be desirable, to achieve differing controlled release profiles.

Many factors influence the extraction of proteins into organic solutions, namely, buffer pH and ionic strength, protein molecular weight, detergent: protein ratios, pI and distribution of charge, as well as surfactant properties and solvent properties. Variation of these parameters may be required to maximise the efficiency of the method steps. This will be apparent to a skilled person.

The parameters may also be varied to achieve differing controlled release properties for the resulting products. For example, the HIP complex:HDC ratio or variations in solvent blends may influence the release properties. Variations in these parameters will also be apparent to the skilled person.

The formulations may be dried by any suitable method, including freeze-drying, oven drying, supercritical fluid processing and, preferably, spray-drying. Spray-drying is preferred as it allows very rapid evaporation of solvent, leaving a glassy amorphous product with low residual solvent level. The glassy amorphous product should preferably be stable at room temperature, or above, to allow easy storage of the compositions without losses in activity.

The dried product should preferably be in a solid form which is storage stable at room temperature, or above. The stability may be attributable to the carbohydrate which forms a glassy amorphous structure on drying. In one embodiment, the product has a glass transition temperature ( $T_g$ ) above 20°C, preferably above 30°C. The product may be in a solid form suitable for direct delivery to a patient. Preferably, the product is a dry powder or "microsphere" having a diameter of less than 30  $\mu\text{m}$ , preferably less than 10  $\mu\text{m}$  and most preferably less than 5  $\mu\text{m}$ . These powders are suitable for pulmonary delivery. The product may also be a microneedle for ballistic or transdermal delivery.

The following Examples illustrate the invention.

Example 1  $\alpha$ -Chymotrypsin (CMT)

$\alpha$ -Chymotrypsin (CMT) is a non-membrane-associated protein which has a pI of 8.5 and a net positive charge between pH 5 and 6. Efficient partitioning of CMT into organic solvent has been achieved when CMT was mixed with 40 equivalents of sodium docusate in 10 mM potassium acetate/ $\text{CaCl}_2$  buffer at pH 5. It was also noted that ionic strength played a very important role in the efficiency of extraction, mainly through control of the formation of emulsions. The ionic strength was controlled by varying the calcium chloride concentration and a general trend emerged, which showed that a decrease in ionic strength resulted in a drop in the percentage recovery of protein into solvent. The choice of organic solvent is important as it has been found, using CD measurements, that CMT was native-like in non-polar solvents such as isooctane, decalin and carbon tetrachloride but had little or no organised structure in more polar solvents such as dichloromethane.

CMT at a concentration of 2mg/ml in 10mM sodium acetate, 5mM calcium chloride, pH 7.0, was mixed with 50 molar equivalents of AOT at a concentration of 1.778mg/ml in hexane. Following centrifugation, the organic layer was isolated, dried in vacuo and the protein concentration determined using the BCA assay. Calculations showed that 80-90% of the enzyme was extracted into the solvent.

This experiment was then repeated with TOAC being present in an organic solvent. TOAC (60mg/ml in acetone) was added to the HIP sample of CMT (2mg/ml in hexane) resulting in a final composition of 30mg/ml TOAC and 1mg/ml CMT in acetone and hexane (1:1). The amount of TOAC used was between 5 and 10 times the amount of enzyme. The resulting solution was spray-dried to form a dry powder composition.

Example 2 Insulin



(i) Insulin (5mg/ml) in 10mM sodium acetate buffer, pH 2.5, was mixed with 4.5 molar equivalents of AOT (10mg/ml) in water, resulting in efficient precipitation of the protein. The protein was isolated by centrifugation and the resultant pellet re-dissolved in a mixture of acetone and IPA (1:2) containing 25mg/ml TOAC or TIBAC. BCA analysis of the dried mixture showed 99% of the protein was recovered in the solvent. Spray-drying the solution gave yields up to 43% and early analysis of the spray-dried material by DSC indicated the presence of a glass.

(ii) Insulin was hydrophobically ion-paired with 7.5 molar equivalents of benzalkonium chloride in 10mM sodium carbonate buffer, pH 11, and redissolved in acetone and IPA (1:2) containing 25mg/ml TOAC. BCA analysis of this formulation revealed 92% of the protein was extracted into solvent. Spray-drying of this formulation resulted in 18% recovery.

(iii) Insulin was also spiked with 2% FITC-labelled insulin, extracted into IPA and acetone (ratio 2:1) containing TOAC using AOT, and spray-dried. The percentage of protein recovered in the solvent was 96%, and spray, drying gave a 35% recovery of material.

### Example 3 $\alpha$ -L-phosphatidylinositol (PPI)

An initial experiment was performed to investigate the optimum amount of PPI required to yield a high recovery of insulin into organic solvent. The amount of PPI was varied from 5 to 7.5 molar equivalents for 2mg samples of insulin. The insulin was dissolved in 10mM sodium acetate buffer, pH 2.5 (2mg/ml), and a solution of 5mg/ml PPI was prepared in water. Precipitation occurred on addition of PPI to each insulin sample and the precipitates were collected by centrifugation at 2500rpm for 2 minutes. The pellets were resuspended in a variety of different solvents, i.e. acetone, dichloromethane, ethanol and mixtures of these. A 90% recovery in the organic solvent was achieved when dichloromethane and ethanol (ratio 1:1) was employed. The precipitate readily dissolved to give a 2mg/ml solution.

Example 4 Insulin with DPPA, DPPG

Two lecithin derivatives were examined as potential surfactants for the HIP of insulin. Standard buffer conditions were used (10mM sodium acetate buffer, pH 2.5) throughout. Optimisation of the conditions required to HIP insulin with DPPA.Na involved varying the molar equivalents of the surfactant from 5 up to 20. The precipitates were dissolved in ethanol:DCM (1:1) and a recovery of 71% was achieved when 9 molar equivalents were used.

The second lecithin derivative to be examined was DPPG.Na. Again, the reaction conditions were optimised by varying the quantity of DPPG added relative to insulin. The quantities investigated ranged from 5 to 12 molar equivalents. Following analysis by the BCA assay, approximately 88% of the protein was recovered in the organic solvent when 8 molar equivalents were used.

Example 5 Leuprolide

In an attempt to broaden the application of HIP, additional test molecules were investigated. The LHRH analogue leuprolide acetate has two possible sites for HIP. Initial experimentation compared the reaction in 10mM sodium acetate buffer, pH 2.5, and 100mM sodium citrate buffer, pH 5. PPI was used as the surfactant, and the addition of 2 molar equivalents resulted in a clear, sticky pellet forming in the sample conducted in acetate buffer. BCA analysis of the pellet resuspended in ethanol:DCM (1:1) revealed 66% of the peptide had been recovered in the acetate sample whilst only 3% was recovered at pH5. A standard curve for the BCA assay using leuprolide was constructed and the reaction repeated. Between 63 and 66% recovery was obtained.

The reaction was also attempted with DPPG.Na. The buffer was kept as 10mM sodium acetate, pH 2.5. Owing to the insolubility of DPPG.Na in water compared with PPI, a range of molar equivalents was examined. The amount of DPPG.Na was varied between 1 and 5 times the amount of peptide. The results indicated that an increase in the

amount of DPPG.Na resulted in an increase in percentage recovery of the peptide. The highest recovery (65%) was achieved when 5 molar equivalents were used.

Example 6 Trypsin

5        Trypsin was also investigated, as an example of an enzyme. The aim was to demonstrate that activity can be maintained following HIP. 2mg/ml trypsin in 10mM sodium acetate buffer, pH 2.5, was mixed with varying molar equivalents of DPPG (from 40x to 100x) and the precipitates  
10        collected. Resuspension in ethanol:DCM (1:1) and subsequent analysis by the BCA assay showed the recoveries ranged from 72% to 83%. The precipitates formed with 90 and 100 equivalents of DPPG were not very soluble in solvent, probably due to the amount of lecithin present.  
15        Further optimisation with 60 molar equivalents of DPPG was attempted.

      A further reaction investigated varying the pH of the acetate buffer from pH 2.5 up to pH 7.3. The best recovery was obtained at pH 2.5. The amount of enzyme taken up into  
20        the organic solvent was 74%. Finally, the initial concentration of the enzyme was increased from the standard 2 mg/ml to 5 and 10 mg/ml. BCA analysis of the redissolved pellets showed approximately 86% had been recovered when the initial enzyme concentration was 5mg/ml.

CLAIMS

1. A method for the preparation of a therapeutic composition, comprising  
forming a solution, in an organic solvent, of a hydrophobically-derivatised carbohydrate (HDC) and an ion-pair complex of a hydrophilic therapeutic agent and an ionic substance; and  
drying the solution.
2. A method according to claim 1, comprising the steps of:
  - (i) mixing the therapeutic agent in aqueous solution with the ionic substance to form the ion-pair complex;
  - (ii) adding a water-immiscible organic solvent to form an organic phase, and allowing the ion-pair complex to pass into the organic phase;
  - (iii) separating the organic phase;
  - (iv) adding the HDC to the organic phase; and
  - (v) drying the organic solution.
3. A method according to claim 1, comprising the steps of:
  - (i) mixing the therapeutic agent with the ionic substance in an aqueous medium, to form a precipitate;
  - (ii) dissolving the precipitate and the HDC in an organic solvent; and
  - (iii) drying the solution.
4. A method according to claim 3, wherein the precipitate is isolated prior to step (ii).
5. A method according to any preceding claim, wherein the therapeutic agent is a protein, peptide or polynucleotide.
6. A method according to any preceding claim, wherein the agent is an enzyme or hormone.
7. A method according to any preceding claim, wherein the agent is insulin.

8. A method according to any preceding claim, wherein the HDC has a carbohydrate backbone and at least one hydroxyl group substituted with a less hydrophilic derivative thereof.

5 9. A method according to any preceding claim, wherein the HDC is selected from sorbitol hexacetate,  $\alpha$ -glucose pentaacetate,  $\beta$ -glucose pentaacetate, 1-O-octyl- $\beta$ -D-glucose tetraacetate, trehalose octaacetate, trehalose octapropanoate, sucrose octaacetate,  $\beta$ -4',6'-diisobutyryl  
10 hexaacetyl lactose, sucrose octapropanoate, cellobiose octaacetate, raffinose undecaacetate, raffinose undecapropanoate and trehalose 6,6-diisobutyrate hexaacetate.

10. A method according to any preceding claim, wherein  
15 drying is carried out by spray-drying.

11. A method according to any preceding claim, wherein the ionic substance is a detergent.

12. A composition comprising, in solid dose form, a hydrophobically-derivatised carbohydrate, a therapeutic  
20 agent and a pharmaceutically acceptable ionic detergent.

13. A composition according to claim 12 obtainable by a method according to any of claims 1 to 11.

14. A composition according to claim 12 or claim 13, wherein the composition is in a glassy, amorphous, form  
25 having a Tg above 20°C.

15. A composition according to any of claims 12 to 14, wherein the solid dose form is particles having a size of less than 10  $\mu\text{m}$ , preferably from 1 to 5  $\mu\text{m}$ .

16. A composition according to any of claims 12 to 14,  
30 wherein the solid dose form is microneedles suitable for ballistic delivery.

17. A composition according to any of claims 12 to 16, for therapeutic use.

18. A device for the pulmonary delivery of a therapeutic  
35 agent, wherein the device includes a composition according to claim 15.

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 00/02661

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K9/16 A61K47/48 A61K38/28 A61K9/14

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS, CHEM ABS Data, MEDLINE, EMBASE

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 29097 A (QUADRANT HOLDINGS CAMBRIDGE ;COLACO CAMILO (GB); SANDERSON IAN (GB) 9 July 1998 (1998-07-09) page 9, last paragraph -page 10, paragraph 2 page 16 examples 7,9 claims 1-8,13-15,20,21 -----	1,5-15, 17,18
A	WO 99 33853 A (QUADRANT HOLDINGS CAMBRIDGE ;BLAIR JULIAN ALEXANDER (GB)) 8 July 1999 (1999-07-08) example 2C -----	1-18



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

### \* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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# INTERNATIONAL SEARCH REPORT

Information on patent family members

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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